J. theor. Biol. (1994) **166**, 9–31

Threshold Conditions for the Spread of the HIV Infection in Age-structured Populations of Homosexual Men

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(*Received on* 10 *April* 1992, *Accepted in revised form on* 17 *March* 1993)

The age-structure of a population, and the distribution of sexual behavior according to age, are significant factors determining the spread of the AIDS epidemic. The threshold conditions for age-structured models account for life-history information, and thus differ significantly from their age-independent counterparts. We examine the threshold conditions for four general age-structured models of the spread of HIV in a homosexual population: three with random partner selection and one with biased partner selection. We consider both discrete and continuous risk groups, and the duration of infection. Susceptibility and infectiousness are treated separately, and the infectivity varies with duration of infection. Through specific examples, we examine the sensitivity of the threshold conditions to the population age-structure and the shape of the infectivity profile. The effects of each are of the same order of magnitude.

1. Introduction

The retrovirus, human immunodeficiency virus (HIV), which causes AIDS has spread into nearly all countries of the world. The most heavily hit regions find themselves essentially under siege by this invariably fatal retrovirus. It has been estimated, for example, that in some regions of central Africa up to 20% of the population is infected (Piot *et al.*, 1990; HIV/AIDS surveillance database), and that in the Bronx in New York City 13% of men and 7% of women aged 25–40 years are infected. AIDS has become one of the top ten leading causes of death in the USA for children ages 1–5 and young adults of both sexes (Chu *et al.*, 1990; Kilborne *et al.*, 1989, 1990; *Morbidity and Mortality Weekly*, 1990). With no cure in sight, the repercussions of this epidemic will be enormous.

HIV is spread almost exclusively by sexual contact, needle-sharing, and blood transfusions, and from mother to infant prior to birth or by breast-feeding. It is occasionally spread by accidents involving blood, and other contact with body fluids, such as the cases in Russia where infection was spread from infants to their mothers via breast-feeding (Pokrovsky *et al.*, 1990).

Different transmission modes are dominant in different regions of the world. Heterosexual intercourse is driving the epidemic in Africa. In the USA and Europe the epidemic has spread primarily by homosexual intercourse and the sharing of needles by intravenous drug users (IVDUs), although there are preliminary indications, such as the highly publicized infection of Magic Johnson, that there is a shift to heterosexual spread in the most heavily hit regions of the USA.

0022–5193/94/010009 + 23 $8.00/0

The biological and sociological factors driving this epidemic are complex. AIDS may occur as early as 2 years after infection, but some infected individuals are symptom-free 12 years after infection. The mean time from infection to AIDS for adults is at least 7 years. The probability that a single sex act will transmit the virus seems to depend on a plethora of poorly understood factors, including age and the presence of other sexually transmitted diseases. The rate and pattern of spread of any sexually transmitted disease is affected by the distribution of partner acquisition rates in the population (Hethcote & Yorke, 1984; Anderson *et al.*, 1986). Homosexual men with high partner acquisition rates are much more likely to be infected with HIV than men with low rates. Social networks and distributions of sexual and drug behaviors in the population are difficult to study, and little good data have been collected.

Mathematical models of the transmission dynamics of HIV have proven useful in providing a logical structure within which to incorporate knowledge and test assumptions about this complex epidemic. Model results demonstrating the important role played by social mixing patterns and variable infectivity have spurred attempts to collect data on these two questions. Model simulations have helped epidemiologists understand such questions as the relative risks presented by oral and anal sex, the reasons for uncertainties in predictions of future AIDS cases, and the interactions between other sexually transmitted diseases and HIV. Transmission models are beginning to help with the design of intervention programs, demonstrating the danger that lies in procrastination: earlier interventions save many more lives than later interventions.

The first models of HIV transmission were published in 1986. Pickering *et al.* (1986) noted that the data on rectal gonorrhea provided an important source of information about sexual behavior change among homosexual men, if it were properly deciphered through a model of its spread. Anderson *et al.* (1986) presented models which accounted for the duration of infection and the continuous variation in sexual behavior, such as the number of sexual partners, seen in sexual behavior studies. Following on the work of Anderson *et al.* (1986), Hyman and Stanley (1988) added an infectivity which depends on the duration of infection and relaxed the assumption of random mixing between people with different risk behaviors. A similar model of biased partner selection was developed by Jacquez *et al.* (1988) for discrete mixing groups. Dietz (1988) presented a model which took a different approach, and looked at the importance of the duration of relationships. Modelers have extended these early models to study the spread of infection by intraveneous drug users, heterosexual sex, and the importance of role separation and behavior changes. Sattenspiel (1990) provides a comprehensive review of many of these developments, as well as of the uses of mathematical models in understanding the transmission dynamics of other infectious diseases.

Models of the spread of infection in African countries by heterosexual sex, blood transfusions, and perinatal transmission include age-structure (Bongaarts, 1989; May *et al.*, 1989; Stanley *et al.*, 1991). Age-structure is an important determinant of sexual activity levels and partner selection. In this paper, we present models for the spread of HIV infection in homosexual populations which imbed the earlier models of Anderson *et al.* (1986) and of Hyman and Stanley (1988) into an age-structured format.

The goal of this paper is to examine, in a preliminary fashion, how age-structure affects the spread of HIV infection. We formulate four models for HIV spread in populations of homosexual men. In these models the population is subdivided into uninfected people, infected people, and people with AIDS. In the first three models, we assume that partners are chosen randomly, which leads to proportionate mixing. The fourth model relaxes this assumption, and allows for special cases of non-random partner selection. We determine the threshold conditions and stability of the infection-free equilibrium for each of these models, and demonstrate the impact of age-structure on these conditions.

The threshold condition specifies critical conditions for an epidemic to grow or die out. The threshold conditions are characterized by the average reproductive number: the average number of secondary infections produced by one infected individual in the early stages of an epidemic. If this average reproductive number exceeds unity, then the infection can maintain itself within the population, otherwise the epidemic dies out (Dietz, 1976, 1985; Anderson, 1982; Anderson & May, 1985, 1987; Diekmann *et al.*, 1989). Analytically derived threshold conditions provide information about the sensitivity of the epidemic to changes in parameters, without the need for a complete numerical exploration of parameter space.

In most simple homogeneous epidemiological models, where all the individuals are assumed to be identical, the average reproductive number can be defined as the product of the transmission probability and the duration of the infectious period. However, in heterogeneous populations the threshold conditions are more complex and additional factors must be included (Hoppensteadt & Murray, 1981; Dietz &

Schenzle, 1985; Castillo-Chavez *et al.*, 1989*a*, *b*; Hethcote *et al.*, 1989). Little theoretical work has been done on complex AIDS models. Of notable exception is the work of Castillo-Chavez and his collaborators (Castillo-Chavez *et al.*, 1989*a*; Thieme & Castillo-Chavez, 1989), who have determined threshold conditions, and other properties, for models with variable duration of infection, and infectivity which varies with the duration of infection; and of Busenberg and Castillo-Chavez (1991), who extend this work to models with age-structure.

In the next three sections of this paper we develop threshold conditions which are similar, but slightly more general than those of Busenberg and Castillo-Chavez (1991). All of these threshold conditions are for models with proportionate mixing. We then develop a threshold result for a model with non-random mixing. We discuss the effect that age-structure has on the mathematical form of the reproductive number, and then use specific examples to examine the sensitivity of the threshold conditions to the age-structure of the population and the distribution of infectivity with duration of infection.

The results we obtain improve our understanding of the complexities behind the AIDS epidemic. However, although these models are more realistic than earlier ones, we have made many simplifying assumptions, and extreme caution must be used in making even qualitative assessments of the epidemic based on these results.

2. The Discrete Risk Group Model

Consider a population of homosexual men who are not in a mutually monogamous life-time relationship and are engaging in sex with other men. This at-risk population consists of uninfected susceptible men, infected men without AIDS, and men with AIDS.

For this first model each infection category is distributed over age and then subdivided by risk level into L discrete classes: $i = 1, 2, \ldots, L$, with $i = 1$ being the risk level with the lowest partner acquisition rates at a given age and $i = L$ the highest (the more realistic continuous-risk case is considered in Section 4). Individuals are assumed to belong to the same risk group throughout their sexually active lifetimes. By neglecting flows between risk groups, we are neglecting the effect of behavior changes resulting from AIDS education and life-cycle events like divorce. We account for some age variations in behavior by allowing the partner-acquisition rate of each risk group to depend on age.

Denote the distribution functions of uninfected and infected people with risk i and age a by $U_i(t, a)$ and $I_i(t, a)$, where t is time. These functions are such that the number of uninfected or infected people in risk group i with ages between a_1 and a_2 is the integral from a_1 to a_2 of $U_i(t, a)$ or $I_i(t, a)$, respectively. We neglect transmission of the virus by men with AIDS (because they form a small portion of the infected population and most are practicing safe sex or have become sexually inactive) and combine all risk groups into one AIDS category $A(t, a)$. We neglect migration between populations, and assume that the only recruitments into the population are a constant inflow of uninfected men. We also assume that all infected people are infectious and will eventually develop AIDS.

Under these assumptions, the dynamics of the population are governed by the following system of equations and associated boundary conditions:

$$\begin{cases} \dfrac{\partial U_i}{\partial t} + \dfrac{\partial U_i}{\partial a} = \Lambda_i(a) - (\mu(a) + \lambda_i(t, a))U_i, \\ U_i(t, a_0) = B_i, \\ U_i(0, a) = \Phi_i(a); \end{cases} \tag{1a}$$

$$\begin{cases} \dfrac{\partial I_i}{\partial t} + \dfrac{\partial I_i}{\partial a} = -(\mu(a) + \gamma(a))I_i + \lambda_i(t, a)U_i, \\ I_i(t, a_0) = 0, \\ I_i(0, a) = \Psi_i(a); \end{cases} \tag{1b}$$

$$\begin{cases} \dfrac{\partial A}{\partial t} + \dfrac{\partial A}{\partial a} = -\delta(a)A + \gamma(a)\displaystyle\sum_{j=1}^{L} I_j, \\ A(t, a_0) = 0, \\ A(0, a) = 0; \end{cases} \tag{1c}$$

where μ = the attrition rate due to natural death or movement out of the sexually active population; λ_i = infection rates; B_i = rate at which uninfected men flow into the i-th risk group at age a_0; $\Lambda_i(a)$ = the rate at which uninfected men flow into the population at ages greater than a_0; γ = rate of developing AIDS; δ = death rate due to AIDS; and Φ_i and Ψ_i are the initial distributions of the uninfected and infected populations.

We consider infection rates that can be represented as

$$\lambda_i(t, a) = \sum_{j=1}^{L} \int_{a_0}^{\infty} \beta_{ij}(a, a')\pi_{ij}(a, a', t)\frac{I_j(t, a')}{N_j(t, a')}\,da', \tag{2}$$

with the total sexually active population in risk group j given by

$$N_j(t, a) = U_j(t, a) + I_j(t, a).$$

Here $\beta_{ij}(a, a')$, the *transmission probability*, is the probability that an infected person of age a' in risk group j will infect an uninfected partner of age a in group i during their partnership; $\pi_{ij}(a, a', t)$ is the rate of pair formation between people of age a in the i-th risk group and people of age a' in the j-th risk group; and I_j/N_j is the probability that a randomly selected partner from the j-th risk group is infected.

We assume the transmission probability is the product of the susceptibility of the uninfected person (the probability that he gets infected given that he is exposed to virus) and the infectiousness of the infected individual (the probability that the infected individual sheds virus). Each of these may depend on the type of contact or the presence of other sexually transmitted diseases, and therefore on the risk groups of the two participants. They may also both depend on age. However, in order to keep the analysis of the model tractable, we allow susceptibility to be age-dependent, but make the somewhat restricting assumption that infectiousness is age-independent. Hence $\beta_{ij} = s_i f_j \beta(a)$ where s_i and f_j are constants which describe the susceptibility of an uninfected individual in the i-th risk group and infectiousness of an infected individual in the j-th risk group.

In order to simplify the analysis, we assume that there are no strong biases at work, and partners are chosen at random, according to their availability (this unrealistic assumption is relaxed in Section 5). The random partner selection process leads to a *proportionate mixing rate*, π_{ij}, of the form

$$\pi_{ij}(a, a', t) = \frac{r_i(a) r_j(a') N_j(t, a')}{\sum_{k=1}^{L} \int_{a_0}^{\infty} r_k(\alpha) N_k(t, \alpha)\, d\alpha}, \tag{3}$$

where $r_i(a)$ is the partner acquisition rate of people of age a in the i-th risk group.

Under these assumptions, the infection rate is

$$\lambda_i(t, a) = \frac{s_i \beta(a) r_i(a)}{\sum_{k=1}^{L} \int_{a_0}^{\infty} r_k(\alpha) N_k(t, \alpha)\, d\alpha} \times \sum_{j=1}^{L} f_j \int_{a_0}^{\infty} r_j(a') I_j(t, a')\, da'. \tag{4}$$

In the absence of infection, $\lambda_i \equiv 0$ and $(U_i(t, a), I_i(t, a), A(t, a)) \to (U_i^0(a), 0, 0)$ as $t \to \infty$, where the steady-state uninfected population is

$$U_i^0(a) = B_i e^{-M(a)} + e^{-M(a)} \int_{a_0}^{a} e^{M(x)} \Lambda_i(x)\, dx, \tag{5a}$$

with

$$M(a) = \int_{a_0}^{a} \mu(s)\, ds. \tag{5b}$$

If this infection-free equilibrium is a stable solution of (1), then introducing a small number of infected people into the equilibrium population will not result in propagation of an epidemic. On the other hand, if the equilibrium is unstable then an initial infection will grow and persist. We proceed to determine the threshold condition which defines the change in stability.

In order to study the stability of this equilibrium, we linearize the system (1) and (4) around $(U_i^0, 0, 0)$. Let $u_i(t, a) = U_i(t, a) - U_i^0(a)$,

$$N_j(t, a) = U_j^0(a) + u_j(t, a) + I_j(t, a) \approx U_j^0(a), \tag{6}$$

and define $\tilde{\lambda}_i(t, a)$ as the linearization of the rate of infection, $\lambda_i(t, a)$:

$$\tilde{\lambda}_i(t, a) = \frac{s_i \beta(a) r_i(a)}{U_T^0 \times \langle r^0 \rangle} \sum_{j=1}^{L} f_j \int_{a_0}^{\infty} r_j(a') I_j(t, a')\, da'. \tag{7}$$

In this expression, U_T^0, is the total uninfected population at the equilibrium, and $\langle r^0 \rangle$ is the mean partner acquisition rate at equilibrium:

$$\langle r^0 \rangle \equiv \frac{1}{U_T^0} \sum_{k=1}^{L} \int_{a_0}^{\infty} r_k(\alpha) U_k^0(\alpha)\, d\alpha, \tag{8a}$$

where

$$U_T^0 \equiv \sum_{k=1}^{L} \int_{a_0}^{\infty} U_k^0(\alpha)\, d\alpha. \tag{8b}$$

The linearized approximation of (1) can now be written as

$$\frac{\partial u_i}{\partial t} + \frac{\partial u_i}{\partial a} = -\mu(a) u_i - \tilde{\lambda}_i(t, a) U_i^0(a), \tag{9a}$$

$$\frac{\partial I_i}{\partial t} + \frac{\partial I_i}{\partial a} = -(\mu(a) + \gamma(a)) I_i + \tilde{\lambda}_i(t, a) U_i^0(a), \tag{9b}$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} = -\delta(a) A + \gamma(a) I_j, \tag{9c}$$

with boundary conditions

$$u_i(t, a_0) = I_i(t, a_0) = A(t, a_0) = 0. \tag{9d}$$

In these equations $A(t, a) \to 0$ as $t \to \infty$ if and only if $I_i(t, a) \to 0$ $(i = 1, 2, \ldots, L)$. Since the dynamics of $A(t, a)$ do not affect the dynamics of $u_i(t, a)$ and $I_i(t, a)$, the behavior of eqns (9a) and (9b) determines the asymptotic behavior of the full system (1).

To estimate the initial growth rate, we assume that the solutions of (9) grow (or decay) exponentially with time:

$$u_i(t, a) = \tilde{u}_i(a) e^{\alpha(t-a)},$$
$$I_i(t, a) = \tilde{I}_i(a) e^{\alpha(t-a)}, \tag{10}$$

where $\tilde{u}_i(a)$ and $\tilde{I}_i(a)$ are functions which describe the age distribution of the population near the trivial equilibrium.

Defining two age-independent functions of the infected populations,

$$w_j = f_j \int_{a_0}^{\infty} r_j(a')\tilde{I}_j(a')e^{-ca'}\,da', \tag{11a}$$

and

$$W = \sum_{j=1}^{L} w_j, \tag{11b}$$

and substituting (10) into (9), we obtain a system of equations for $\tilde{u}_i(a)$ and $\tilde{I}_i(a)$:

$$\frac{d\tilde{u}_i(a)}{da} = -\mu(a)\tilde{u}_i(a) - b_i(a)e^{ca}W, \tag{12a}$$

$$\frac{d\tilde{I}_i(a)}{da} = -(\mu(a)+\gamma(a))\tilde{I}_i(a) + b_i(a)e^{ca}W. \tag{12b}$$

The age- and risk-dependent coefficients, $b_i(a)$, are given by

$$b_i(a) = s_i\beta(a)\hat{r}_i(a)\hat{U}_i^0(a), \tag{12c}$$

where we have normalized the equilibrium population distribution by the total equilibrium population, and the partner acquisition rate by the mean partner acquisition rate:

$$\hat{U}_i^0(a) \equiv \frac{U_i^0(a)}{U_T^0}, \quad \hat{r}_i(a) \equiv \frac{r_i(a)}{\langle r^0\rangle}. \tag{13}$$

From this we see that the $b_i(a)$ are known quantities which are all independent of the growth rate c.

Solving (12b) for $\tilde{I}_i(a)$, we have

$$\tilde{I}_i(a) = W\int_{a_0}^{a} P(a,s)b_i(s)e^{cs}\,ds, \tag{14a}$$

where

$$P(a,s) = \exp(-M(a) - \Gamma(a) + M(s) + \Gamma(s)), \tag{14b}$$

$$\Gamma(a) = \int_{a_0}^{a} \gamma(v)\,dv. \tag{14c}$$

Note that if a person is infected at age a', then $e^{-\Gamma(a)+\Gamma(a_1)}$ is the probability that he has not developed AIDS by age a.

By substituting (14) into (11a), we obtain a new expression for w_i:

$$w_i = Wf_i\int_{a_0}^{\infty}\hat{r}_i(a)\int_{a_0}^{a} P(a,s)b_i(s)e^{-c(a-s)}\,ds\,da. \tag{15}$$

Summing this over i and substituting into (11b) gives an equation for W in terms of itself, which allows us to define the threshold condition for stability of the infection-free equilibrium:

$$W = W\langle r^0\rangle\sum_{i=1}^{L} f_i\int_{a_0}^{\infty}\hat{r}_i(a) \times\int_{a_0}^{a} P(a,s)e^{-c(a-s)}b_i(s)\,ds\,da \equiv WR(c). \tag{16}$$

There exists non-zero solutions W to (16) if and only if $R(c)=1$ for some c. In order to determine under what conditions the curve $R(c)$ crosses 1, note that

$$\frac{dR(c)}{dc} = -\langle r^0\rangle\sum_{i=1}^{L} f_i\int_{a_0}^{\infty}\hat{r}_i(a) \times\int_{a_0}^{a} P(a,s)e^{-c(a-s)}(a-s)b_i(s)\,ds\,da \tag{17}$$

is always negative if any $U_i^0(a)$ is non-zero. Therefore $R(c)$ is monotonically decreasing. Since $R(c)\to\pm\infty$ as $c\to\pm\infty$, $R(c)=1$ at some unique real root c^*. If $R(0)<1$ this root is negative, and $I_j(t,a) = \tilde{I}_j(a)e^{c^*(t-a)}\to 0$ as $t\to\infty$. Using $\tilde{I}_j(a)$ from (14) and solving for $\tilde{u}_j(a)$, as $t\to\infty$, we have that $u_j(t,a)\to 0$, $I_j(t,a)\to 0$ and, therefore, $A(t,a)\to 0$, which gives the stability of the equilibrium. Similarly, if $R(0)$ is greater than 1, then $c^*>0$ and the equilibrium $(U_i^0(a),0,0)$ is unstable.

Summarizing the above, we have

2.1. THEOREM: *Define the reproductive number for eqn* (1) *to be*

$$\bar{R} = \frac{\sum_{i=1}^{L}\left\{s_if_i\int_{a_0}^{\infty} r_i(a)\int_{a_0}^{a}\beta(\psi)r_i(s)P(\psi,a)U_i^0(\psi)\,d\psi\,da\right\}}{\sum_{i=1}^{L}\int_{a_0}^{\infty} r_i(a)U_i^0(a)\,da}. \tag{18a}$$

where $U_i^0(a)$ is given by eqn (5). *Then if $\bar{R}>1$, the AIDS epidemic persists, if $\bar{R}<1$, the epidemic dies out.*

Note that $\bar{R}$ is independent of the total initial size of the uninfected population and it can be rewritten in terms of the normalized quantities defined in eqn (13) as

$$\bar{R} = \langle r^0\rangle\sum_{i=1}^{L}\left\{s_if_i\int_{a_0}^{\infty}\int_{a_0}^{a}\beta(\psi)\hat{r}_i(a) \times\hat{r}_i(\psi)P(\psi,a)\hat{U}_i^0(\psi)\,d\psi\,da\right\} \tag{18b}$$

where the population size cancels out. The factor $\langle r^0 \rangle$ indicates that $\bar{R}$ increases with the mean risk in the population. $\bar{R}$ also increases with increasing transmission probabilities and with increasing time from infection to AIDS (the incubation period $1/\gamma$). (Note that the relative susceptibility s_i and the relative infectiousness f_i appear as a product and thus play the same role.) If the parameters μ, γ, r_i, and β are all independent of age and the susceptibility and transmissibility are independent of risk ($s_i = 1, f_i = 1$), then our result reduces to that of the age-independent model of Anderson *et al.* (1986), namely that

$$\bar{R}_A = \frac{E(r^2)}{\langle r^0 \rangle} \frac{\beta}{\mu + \gamma}, \tag{19}$$

where $E(r^2)$ is the second mean of the risk, $\sum_{i=1}^{L} r_i^2 \int_{a_0}^{\infty} \hat{U}_i^0(\psi)\, d\psi$. This well-known formula shows that the variance in the risk affects the threshold condition as much as the mean risk. Often, eqn (19) has been assumed to express the reproductive number for any random-mixing AIDS model. However, as we shall demonstrate in Example (i), the actual reproductive number for our age-structured model given by eqn (18) is significantly more complex than $\bar{R}_A$ because the mean duration of infection, mean transmissibility, and risk behavior interact.

To understand the effect of age structure on the reproductive number, we will perform a few manipulations on eqn (18b). Because $P(\hat{a}, a)$ is the probability that a person who is infected at age $\hat{a}$ is still in the infected population at age a,

$$p_i(\hat{a}) \equiv \int_{\hat{a}}^{\infty} r_i(a) P(\hat{a}, a)\, da \tag{20}$$

is the mean number of partners a person in risk group i will have after infection at age $\hat{a}$.

Switching the order of integration in eqn (18b) and using definition (20) gives

$$\bar{R} = \sum_{i=1}^{L} \left\{ \int_{a_0}^{\infty} \beta(\hat{a}) s_i \hat{r}_i(\hat{a}) \hat{U}_i^0(\hat{a}) f_i p_i(\hat{a})\, d\hat{a} \right\}. \tag{21}$$

Analyzing this equation, we see that $s_i \hat{r}_i(a)$ is, in a sense, the exposure risk of infection being taken by uninfected members of group i of age a relative to the mean population risk. Upon infection, the number of people that they will put at risk is their infectivity times their future number of partners, $\beta(a) f_i p_i(a)$. These factors multiply the fraction of the initial population in that age/risk category to give the fraction of the population that will be at risk due to group i. Summing over all groups and ages then gives the reproductive number.

Even in the absence of age-biased partner choice, age has a strong influence on $\bar{R}$ since older people will have fewer future partners than younger ones. Thus the infection of older people has a smaller effect on $\bar{R}$ than the infection of younger people. Age also enters through the susceptibility and the current risks being taken. These effects can be compounded. For example, if younger people are more susceptible and more likely to have many future partners than older people, then these factors together increase the reproductive number more than each taken separately.

The effects of age are further illustrated in the following two examples.

EXAMPLE (i)

Suppose that the attrition rate, μ, the rate of developing AIDS, γ, and the transmission probability, $\beta s_i f_j$, are all independent of age and risk group. Suppose, furthermore, that the partner acquisition rates, $r_i(a)$, vary slowly with age, and remain close to their value at the minimum age, a_0. This slow variation can be mathematically specified by letting ϵ be a small parameter and by assuming that

$$r_i(a) = r_{i0} + \epsilon r_{i1}(a) \tag{22}$$

where $r_{i1}(a)$ remains small compared to ϵ^{-1} for all a, and $r_{i1}(a_0) = 0$.

Under these assumptions, the mean number of people an infected person will put at risk is

$$p_i(a) = \frac{r_{i0}}{\mu + \gamma} + \epsilon p_{i1}(a) \tag{23a}$$

where

$$p_{i1}(a) = \int_a^{\infty} r_{i1}(x) e^{-(\mu+\gamma)(x-a)}\, dx. \tag{23b}$$

Defining $\langle r_0 \rangle$ to be the mean risk when epsilon is zero, $\langle r_1 \rangle$ to be the mean value of the perturbations r_{i1}, and expanding the reproductive number in ϵ, we have

$$\bar{R} \sim \bar{R}_0 + \epsilon \frac{\beta s f}{\langle r_0 \rangle} \sum_{i=1}^{L} r_{i0} \int_{a_0}^{\infty} \left(p_{i1}(\hat{a}) + \frac{r_{i1}(\hat{a})}{\mu + \gamma} - \frac{r_{i0}}{\mu + \gamma} \frac{\langle r_1 \rangle}{\langle r_0 \rangle} \right) \hat{U}_i^0(\hat{a})\, d\hat{a}, \tag{24}$$

as $\epsilon \to 0$. Here $\bar{R}_0$ is the reproductive number that would result if the partner acquisition rates were equal to the rates at a_0.

The Anderson *et al.* formula, $\bar{R}_A$ of eqn (19), is a poor approximation for the reproductive number in an age-structured population with unbiased partner selection. $\bar{R}_A$ is the product of the probability of

transmission, the mean duration of infection, and the ratio of $E(r^2)$ to $\langle r^0 \rangle$, and can be expressed as

$$\bar{R}_A \sim \bar{R}_0 + \epsilon \frac{\beta s f}{\langle r^0 \rangle (\mu + \gamma)} \sum_{i=1}^{L} r_{i0} \times \int_{a_0}^{\infty} \left(2r_{il}(\hat{a}) - r_{i0} \frac{\langle r_1 \rangle}{\langle r_0 \rangle} \right) \hat{U}_i^0(\hat{a})\, d\hat{a}, \quad (25)$$

as $\epsilon \to 0$. The difference between this "expected" $\bar{R}_A$ and the actual reproductive number $\bar{R}$ is, to order ϵ,

$$\bar{R} - \bar{R}_A \sim \epsilon \frac{\beta s f}{\langle r_0 \rangle} \sum_{i=1}^{L} r_{i0} \int_{a_0}^{\infty} \left(p_{il}(\hat{a}) - \frac{r_{il}(\hat{a})}{\mu + \gamma} \right) \times \hat{U}_i^0(\hat{a})\, d\hat{a}. \quad (26)$$

Replacing p_{il} with its definition, we see that this difference depends on the term

$$p_{il}(a) - \frac{r_{il}(a)}{\mu + \gamma} = \int_a^{\infty} (r_{il}(x) - r_{il}(a)) e^{-(\mu+\gamma)(x-a)}\, dx. \quad (27)$$

If $r_{il}(a)$ varies substantially with age, these terms cannot be neglected when estimating the reproductive number. For example, it may be that sexual activity declines with age, causing the differences to all be negative and significantly reducing the reproductive number below $\bar{R}_A$. On the other hand, if partner acquisition rates first increase after age a_0 and then decrease (in a given risk group), the impact is more difficult to predict.

To demonstrate more clearly the impact of age-structure, we choose a specific set of parameters, and plot the actual and "expected" (i.e. $\bar{R}_A$) reproductive number in the next example.

EXAMPLE (ii)

In this example all functions are chosen so that we can analytically calculate the reproductive number (see Appendix).

Suppose that

$$\mu = \tfrac{1}{15}\,\text{yrs}^{-1}, \quad \gamma = 0{\cdot}1\,\text{yrs}^{-1}, \quad a_0 = 12\,\text{yrs}, \quad s_i f_i \beta(a) = 0{\cdot}1 \quad (28)$$

so that the mean duration of sexual activity is 15 years, the mean time from infection to AIDS is 10 years, 12 is the minimum age of sexual activity, and β, f, and s are independent of age and risk, with transmission occurring in one-tenth of the partnerships. Suppose furthermore that no men enter the sexually active population before age 12 ($B_i = 0$), and that after age 12 men enter the sexually active population at a rate which increases from zero at age 12 to a maximum at age $\alpha_m + 12$, and then slowly decreases back to zero:

$$\Lambda_i(a) = C_m 2^{-3i}(a - 12) e^{-(a-12)/\alpha_m}, \quad i = 0, 1, 2, \ldots, \quad \text{for } a > 12\,\text{yrs}. \quad (29)$$

The constant C_m defines the total population size and scales out of the reproductive number. Note that we have assumed that the fraction of people entering each risk level is independent of age. This is consistent with observations that the distribution functions for sexual behavior have a similar functional form for all populations, even though the parameters which determine the mean and variance are different from one population to the next.

Similarly, we assume that the partner acquisition rate in risk group i also increases from zero at age 12 to a maximum at $\alpha_r + 12$ and then gradually decreases:

$$r_i(a) = 2^i C_r (a - 12) e^{-(a-12)/\alpha_r}, \quad \text{for } a > 12\,\text{yrs}. \quad (30)$$

Following Colgate *et al.*, (1989) we have chosen to distribute the incoming population into risk groups with mean risk $r_{i+1} = 2r_i$, and size $U_{i+1}^0 = U_i^0/8$ in order to be consistent with the distribution found in many sexual behavior surveys. For moderate to high-risk behaviors this distribution has the form r^{-n}, where r is the partner acquisition frequency and n is between 3 and 4 (see Hyman & Stanley, 1988). This distribution has the notable feature that there is a high variance to mean ratio. We have used this, and assumed that the i-th group runs from $r = 2^i$ to $r = 2^{i+1}$ and taken $n = 4$ to obtain the dependence on i of this example.

This choice of functions allows us to obtain an analytical expression for the reproductive number. These calculations are presented in the Appendix. For this example, it is easy to see that the initial growth rate, c^*, increases monotonically with the reproductive number. The argument goes as follows: c^* is the unique root of $R(c) = 1$, where $R(c)$ is defined by eqn (16) and $R(0)$ is the reproductive number. Since γ is a constant, c only appears in the expression for $R(c)$ in the form $\gamma + c$. We thus can write $R(c) = g(\gamma + c)$, and $R(0) = \bar{R} = g(\gamma)$. $R(c)$ is a monotonically decreasing function of c, so $g(x)$ is monotonically decreasing in x, and $\gamma = g^{-1}(\bar{R})$ is monotonically decreasing in $\bar{R}$. Then $c^* = g^{-1}(1) - \gamma = g^{-1}(1) - g^{-1}(\bar{R})$ is monotonically increasing in $\bar{R}$.

Figure 1 shows the distribution of the equilibrium population by age for different values of the most likely entrance age, $\alpha_m + 12$. For populations where most people enter very young, the population distribution is sharply peaked, while for populations with

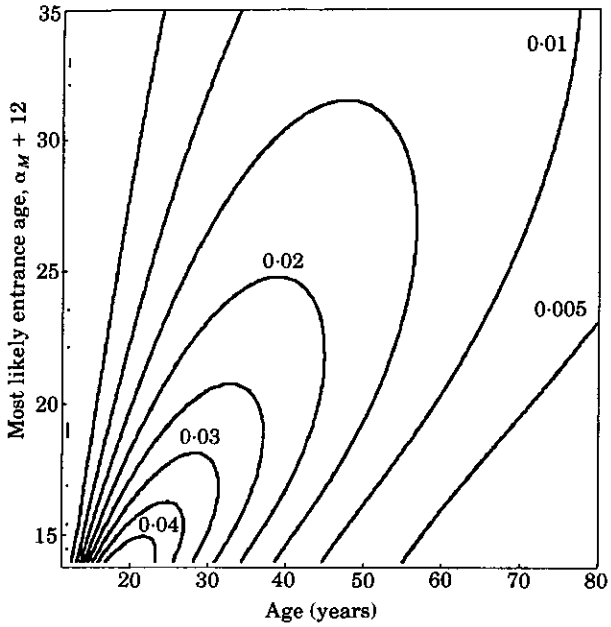

FIG. 1. The distribution of the population in the absence of infection for examples (ii) and (iii) varies with the most likely age of entering the population. The contour level lines, spaced at intervals of 0·005 yrs^{-1}, show the population density in age as given by eqn (A.2) divided by (A.3). The density distribution for a fixed value of the entrance parameter α_m is given by the values along a line parallel to the x-axis. Because most people are entering before age 20, the distribution is sharply peaked when α_m is small. It broadens as α_m increases and people enter over a broader range of ages. Note that, for a fixed value of α_m, the peak of the distribution occurs at an age greater than $\alpha_m + 12$, when the inmigration balances the constant outmigration.

older entrants it is broadly distributed. Note that eqn (29) implies that the distribution of each risk group over age is identical.

Figure 2 shows the dependence of the population mean risk (measured by new partners per year) on the most active age, $\alpha_r + 12$, and the most likely age of entrance into the population, $\alpha_m + 12$. Note that the mean risk increases rapidly, and nearly linearly, with the most active age, and only weakly depends on the age structure of the migration.

The reproductive number increases linearly with the mean risk of the population and the transmission probability, $sf\beta$. To understand how the age-structure affects $\bar{R}$, independent of this effect, we hold the mean risk of the equilibrium population fixed as the parameters α_m and α_r are varied (this is done through the appropriate choice of C_r). In Fig. 3 we show the distribution of sexual behavior in the population, as it depends on the most active age, $\alpha_r + 12$, for a population with $\alpha_m = 5$. From Fig. 1 we see that this population distribution increases rapidly to a maximum at around age 26, and then slowly decays. The largest group of sexually active men is found in the mid-20s. The activity in this population is primarily at young ages when α_r is small, and becomes broadly distributed when it is large. There is a trade-off between activity levels at given ages and numbers of people, as seen in Fig. 3.

In Fig. 4 we show the dependence of the reproductive number on the age structure of the population, and the age structure of behavior. Most of this behavior can be explained by the average number of partners that men will have after infection, if infected at the most active age, $p_i(\alpha_r + 12)$, from eqn (20). $p_i(\alpha_r + 12)$ and the reproductive number have a very similar functional dependent on α_m and α_r. A population which is active primarily at young ages will still continue to have many partners after the most active age, creating a broader dissemination of the infection than one which is active at older ages, given that each population has the same mean risk. Likewise, a population which is older also has more partners after the most active age. This dependence is reversed at larger values of α_r. Since the initial growth rate increases monotonically with the reproductive number, for this example, the initial spreading of the disease depends heavily on the number of partners an infected person is likely to have after infection.

Finally, in Fig. 5 we show the danger involved in drawing conclusions which are based on assuming that the reproductive number calculated for one model can be used for another model. We have used the Anderson *et al.* approximate formula to calculate an "expected" reproductive number, $\bar{R}_A$, and

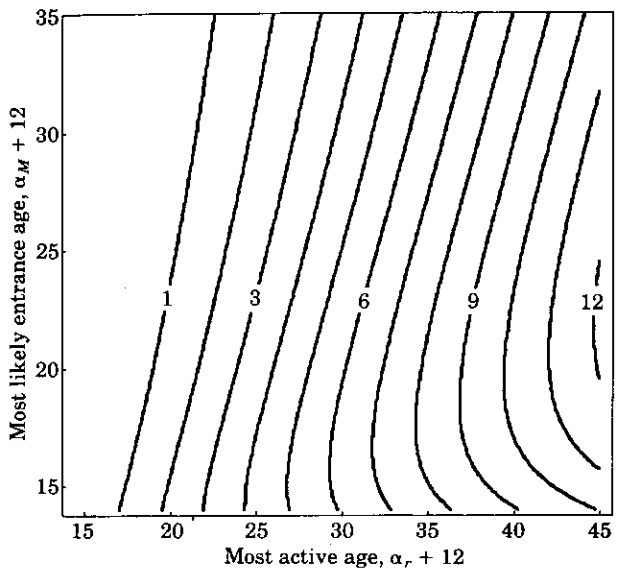

FIG. 2. The mean risk of the population at the infection-free equilibrium, eqn (A.4), for examples (ii) and (iii), as a function of the most active age, $\alpha_r + 12$, and the most likely age of entrance, $\alpha_m + 12$. Contour levels run from 1 to 12 partners per year and $C_r = 1$ partner per year.

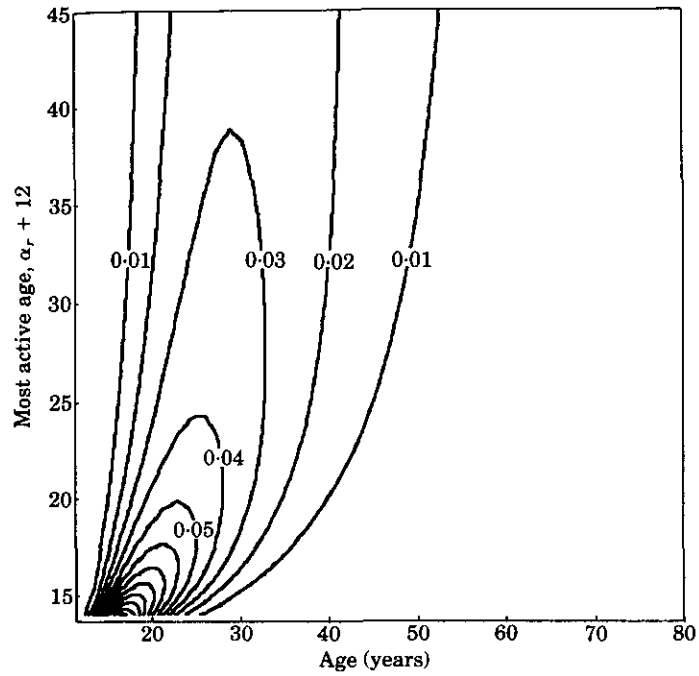

FIG. 3. The distribution over age of partner acquisitions in the population, eqn (A.6), as it varies with α_r for examples (ii) and (iii). Here $\alpha_m = 5$ (a most-likely entrance age of 17), and C_r is determined from eqn (A.5) to ensure that the total population has a fixed mean risk of 1 partner per year, for every choice of α_r. Contour levels are spaced at intervals of 0·01 and run from 0·01 to 0·13 partners per square years. Note that this distribution gets broader with larger α_r, but is generally weighted towards lower ages because of the young age profile of this population: at larger values of α_m, with an older population, the peaks occur near age 26, where there are the most people.

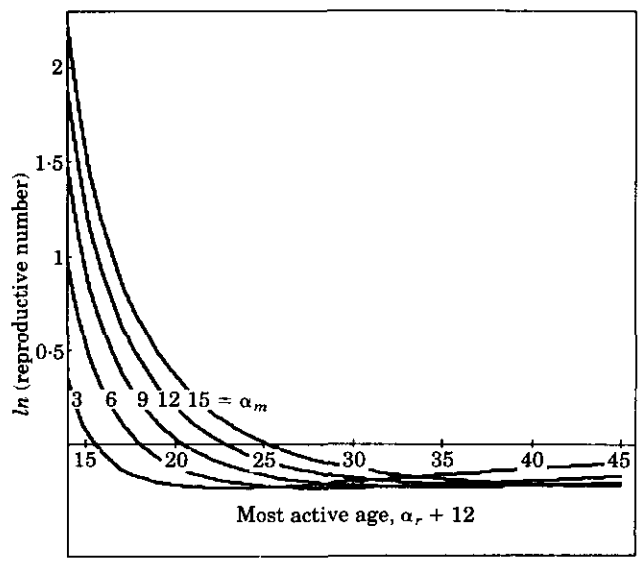

FIG. 4. The dependence of the reproductive number for Example (i) on the most likely age entrance age, $\alpha_m + 12$, and the most active age, $\alpha_r + 12$. Here C_r is varied according to eqn (A.5), so that the mean risk of the population is 2 partners per year for all values of α_m and α_r, and the reproductive number is given by eqn (A.7). Recall that the epidemic will not spread if the reproductive number is less than 1. The initial epidemic is very sensitive to α_r. For a given α_m, and a fixed population structure, α_m determines how the sexual behavior is distributed in the population, as shown in Fig. 3. The epidemic spreads most rapidly in populations in which the sexual activity is concentrated in the younger members of the active population, who must be very active in order to maintain the population mean, and who have many years to transfer infection after they become infected. However, increasing α_m, which both increases the average age and broadens the age-distribution of the population, also increases the strength of the epidemic, at low α_r. This effect is reversed at large α_r.

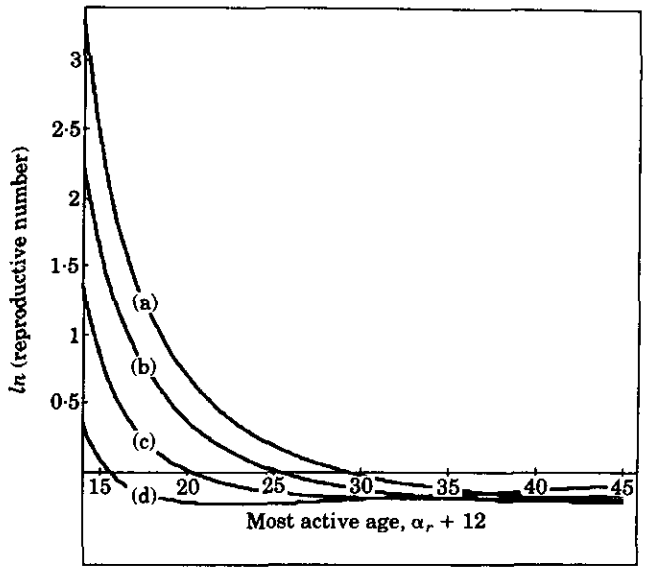

FIG. 5. A comparison between the behavior of the actual reproductive number for example (ii), $\bar{R}$, and the Anderson *et al.* formula, $\bar{R}_A$. As in Fig. 4, the mean risk is held fixed at 2 partners per year. (a) $\bar{R}_A$ for $\alpha_m = 15$ yrs; (b) $\bar{R}$ for $\alpha_m = 15$ yrs; (c) $\bar{R}_A$ for $\alpha_m = 3$ yrs; (d) $\bar{R}$ for $\alpha_m = 3$ yrs. The dependence on population structure is similar for both $\bar{R}$ and $\bar{R}_A$. However, for small values of α_r the age-structure decreases the likelihood of an epidemic, while at large values it slightly increases the possibility of a sustainable epidemic.

compared this to the actual reproductive number, $\bar{R}$. The actual and expected reproductive numbers are significantly different, with age-structure effects generally decreasing initial spread rates.

3. Duration of Infection

Nearly all adults are free of AIDS symptoms for the first 2 years after infection, and the probability of developing AIDS slowly rises after that. This can be modeled by assuming that the probability of developing AIDS depends on the duration of infection (Anderson *et al.*, 1986).

It has been postulated that the infectiousness of individuals carrying HIV depends on the clinical status of the individual, with a short burst of infectiousness occurring shortly after infection, after which infectiousness is generally low until the immune system begins to be seriously affected. Although viral loads and infectiousness are not necessarily directly linked, there is accumulating evidence for this theory. Circumstantial evidence is also provided by transmission studies: estimates of infectiousness which allow this variation have obtained significantly better fits to the data than those which do not (Longini *et al.*, 1989; Jewell & Shiboski, 1990). Since the probability of any particular clinical status depends on how long a person has been infected, infectiousness may in turn be modeled as depending on the duration of infection.

Hyman & Stanley (1988, 1989) and Blythe & Anderson (1988) showed through numerical simulations that it is important to account for these duration of infection effects. Castillo-Chavez *et al.* (1989*a*, *b*) have examined the impact of these effects on the reproductive number. Also, Thieme & Castillo-Chavez (1989) have shown that adding the duration of infection to a model which cannot support oscillations opens up the possibility for long-term oscillations in the population sizes (see also Castillo-Chavez *et al.*, 1989*a*). Intuitively, the 2-year delay before developing AIDS implies a greatly increased pool of infected people as compared to an exponential distribution of times from infection to AIDS. The variation of infectivity with duration implies that time scales are lengthened, except among groups of people who tend to have multiple sexual partners during time intervals which are small compared with the duration of the first infectious burst. Here we examine the impact that this dependent on duration of infection has on the reproductive number for an age-structured model.

Let τ be the duration of infection, and $I_i(t, a, \tau)$ be the distribution of infected people in risk group i over duration of infection and age a. Except for τ dependence, the model is the same as that of the previous section. Duration of infection behaves mathematically the same way that age does: there is a progression of infected people along increasing duration of infection, and a boundary condition at $\tau = 0$, where all newly infected people enter the infected population.

The modified equations are:

$$\begin{cases} \dfrac{\partial U_i}{\partial t} + \dfrac{\partial U_i}{\partial a} = \Lambda_i(a) - (\mu(a) + \lambda_i(t,a))U_i, \\ U_i(t, a_0) = B_i, \\ U_i(0, a) = \Phi_i(a). \end{cases} \tag{31a}$$

$$\begin{cases} \dfrac{\partial I_i}{\partial t} + \dfrac{\partial I_i}{\partial a} + \dfrac{\partial I_i}{\partial \tau} = -(\mu(a) + \gamma(\tau, a))I_i, \\ I_i(t, a_0, 0) = 0, \\ I_i(t, a, 0) = \lambda_i(t, a)U_i, \\ I_i(0, a, \tau) = \Psi_i(a, \tau). \end{cases} \tag{31b}$$

$$\begin{cases} \dfrac{\partial A}{\partial t} + \dfrac{\partial A}{\partial a} = -\delta(a)A \\ \qquad\qquad + \displaystyle\sum_{j=1}^{L} \int_0^{a-a_0} \gamma(\tau, a) I_j(t, a, \tau)\, d\tau, \\ A(t, a_0) = 0, \\ A(0, a) = 0. \end{cases} \tag{31c}$$

Note that the rate of developing AIDS, $\gamma(\tau, a)$, now depends on both duration of infection and age. Under the assumption that the partner acquisition rate is independent of the duration of infection, and that partners are selected independent of their duration of infection, eqn (2) for the rate of infection generalizes to

$$\lambda_i(t, a) = \sum_{j=1}^{L} \int_{a_0}^{\infty} \int_0^{a'-a_0} \beta_{ij}(a, a', \tau)\pi_{ij}(a, a', \tau) \times \frac{I_j(t, a', \tau)}{N_j(t, a')} d\tau\, da' \tag{32}$$

where the total sexually active population of age a' is

$$N_j(t, a') = U_j(t, a') + \int_0^{a'-a_0} I_j(t, a', \tau)\, d\tau,$$

and where $\beta(a, a', \tau)$ is the probability of transmission from a person of age a' and duration of infection τ during a relationship with an uninfected person of age a. Note that no person can be infected longer than the maximum possible time that he has spent in the sexually active population, so that $\tau \leqslant a - a_0$. As before, we make two further assumptions which simplify the analysis of the reproductive number.

First, we assume the probability of infection is separable into four factors,

$$\beta_{ij} = s_i f_j \beta(a)\kappa(\tau).$$

Here the new factor, $\kappa(\tau)$, is a transmission factor which accounts for variations in infectiousness as the disease progresses. Second, we continue to assume that mixing is proportionate and that π_{ij} has the same form as in eqn (3). These two assumptions give a simplified expression for the rate of infection

$$\lambda_i(t, a) = \frac{s_i \beta(a) r_i(a)}{\displaystyle\sum_{k=1}^{L} \int_{a_0}^{\infty} r_k(\alpha) N_k(t, \alpha)\, d\alpha} \times \sum_{j=1}^{L} f_j \int_{a_0}^{\infty} \int_0^{a'-a_0} r_j(a')\kappa(\tau) I_j(t, a', \tau)\, d\tau\, da'. \tag{33}$$

The infection-free equilibrium of system eqns (31) and (33) is again given by eqn (5). Linearizing around this equilibrium, with $u_i(t, a) = U_i(t, a) - U_i^0(a)$, gives

$$\frac{\partial u_i}{\partial t} + \frac{\partial u_i}{\partial a} = -\mu(a)u_i - \tilde{\lambda}_i(t, a)U_i^0(a) \tag{34a}$$

$$\begin{cases} \dfrac{\partial I_i}{\partial t} + \dfrac{\partial I_i}{\partial a} + \dfrac{\partial I_i}{\partial \tau} = -(\mu(a) + \gamma(\tau, a))I_i, \\ I_i(t, a, 0) = \tilde{\lambda}_i(t, a)U_i^0(a), \end{cases} \tag{34b}$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} = -\delta(a)A + \sum_{j=1}^{L} \int_0^{a-a_0} \gamma_j(\tau) I_j(t, a, \tau)\, d\tau. \tag{34c}$$

where $\tilde{\lambda}_i(t, a)$ is given by eqn (33) with $N_i(t, a)$ replaced by $U_i^0(a)$.

As before, the first two eqns (34a) and (34b) are sufficient to determine the asymptotic behavior of the full system.

Assuming that the solution initially changes exponentially, substituting

$$\begin{cases} u_i(t, a) = \tilde{u}_i(a)e^{c(t-a)} \\ I_i(t, a, \tau) = \tilde{I}_i(a, \tau)e^{c(t-a)}, \end{cases} \tag{35}$$

into eqn (34), and solving for $\tilde{I}_i(a, \tau)$, gives

$$\tilde{I}_i(a, \tau) = \tilde{I}_i(a - \tau, 0)e^{-\Delta(a, \tau)} \tag{36a}$$

where

$$\Delta(a, \tau) = \int_0^{\tau} (\gamma(v, v + a - \tau) + \mu(v + a - \tau))\, dv. \tag{36b}$$

Here $\tilde{I}_i(a - \tau, 0)$ is determined by the rate of infection.

Following a procedure similar to that of Section 2, we define

$$w_i = f_i \int_{a_0}^{\infty} \int_0^{a'-a_0} r_j(a')\kappa(\tau)\tilde{I}_i(a', \tau)e^{-ca'}\, d\tau\, da' \tag{37}$$

and take W to be the sum of all of the w_i. Then

$$\tilde{I}_i(x, 0) = \frac{s_i}{S}\beta(x)r_i(x)U_i^0(x)e^{cx}W. \tag{38}$$

By following the approach in Section 2, we can determine the reproductive number for the AIDS model (31):

$$\bar{R} = \frac{\sum_{j=1}^{L} s_j f_j \int_{a_0}^{\infty} r_j(a) \int_0^{a-a_0} \kappa(\tau)\beta(a-\tau) r_j(a-\tau) e^{-\Delta(a,\tau)} U_j^0(a-\tau)\, d\tau\, da}{\sum_{j=1}^{L} \int_{a_0}^{\infty} r_j(a) U_j^0(a)\, da}. \tag{39}$$

As in Section 2, the epidemic spreads if infection is introduced into an uninfected population when $\bar{R} > 1$, and will not spread if $\bar{R} < 1$. We show in example (iii) that the reproductive number depends on the manner in which the infectivity varies with the duration of infection, even when the mean infectivity over the course of infection remains unchanged. The time-dependent behavior might be even more sensitive to these variations, as has been seen in numerical simulations (Hyman & Stanley, 1988).

EXAMPLE (iii)

In this example, we assume that all parameters are the same as in example (ii), except for the rate of developing AIDS, and the factor $\kappa(\tau)$, which defines the dependence of the infectivity on the duration of infection. To demonstrate our point, we use an unrealistic choice for $\gamma(\tau)$: we assume that there is a delay of z years after infection, during which the rate of developing AIDS is zero, and that after z years the rate of developing AIDS is constant, at γ_1:

$$\gamma(\tau, a) = \begin{cases} 0 & \text{if } \tau < z, \\ \gamma_1 & \text{if } \tau \geqslant z. \end{cases} \tag{40}$$

This defines a hazard function which partly captures one of the principle features of the development of AIDS: the long delay after infection before symptoms appear. However, since the development of AIDS after the first 2 years will be exponentially distributed with this choice of $\gamma(\tau)$, this distribution is not accurate, and will underestimate the impact of the duration of infection.

In order to examine the impact that a variable infectivity can have on the epidemic, we use a function which captures some of the features of the most popular hypothesis: a short burst of infectiousness soon after infection, before antibodies appear, a long period of low infectiousness during the asymptomatic

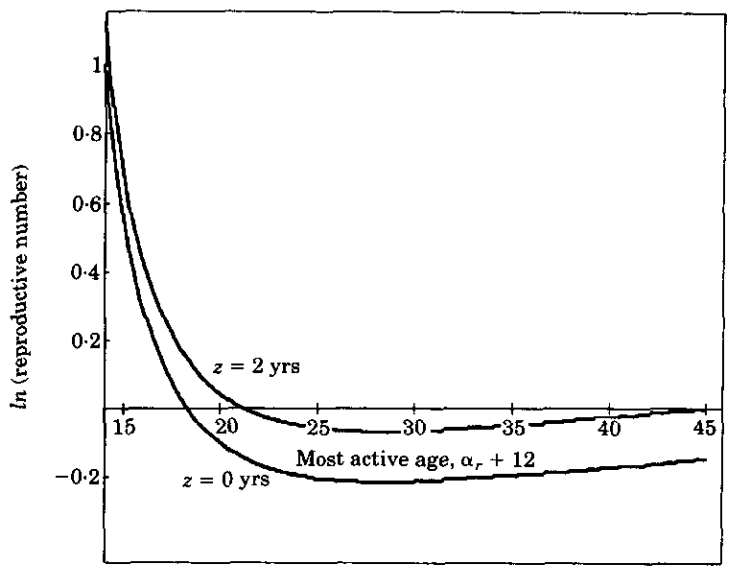

FIG. 6. The effect of the hazard function eqn (40), which describes the distribution of times from infection to AIDS, on the reproductive number, eqn (39), of example (iii). In both cases the mean risk is held fixed at two partners per year and the mean duration of sexually active infection is 6.2 years. The infectivity per contact is independent of the duration of infection. The 2-year delay before the development of AIDS, described by the $z = 2$ case, substantially increases the probability of a growing epidemic compared to the $z = 0$ cases in example (ii).

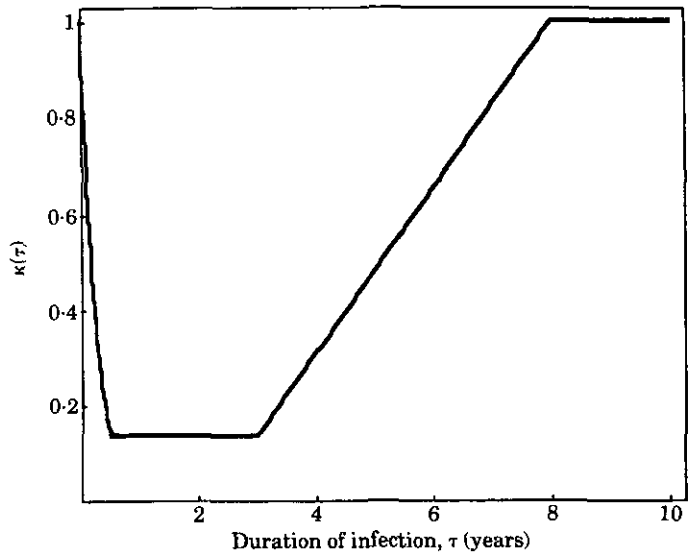

FIG. 7. The functional dependence of the infectivity on the duration of infection used in Figs 8 and 9. The infectivity is high for the first few months. It then remains at a low level until about 5 years after infection, and then slowly increases to the high level again. This infectivity is then scaled by a constant multiplier, so that the mean probability of transmission per partner is 0·05.

phase, and higher infectiousness towards the end of infection. We take $\kappa(\tau)$ to be

$$\kappa(\tau) = \begin{cases} e^{-\tau/k_1} & \text{if } \tau < \tau_1, \\ e^{-\tau_1/k_1} & \text{if } \tau_1 \leqslant \tau < \tau_2, \\ e^{-\tau_1/k_1} + (k_2 - e^{-\tau_1/k_1}) \dfrac{\tau - \tau_2}{\tau_3 - \tau_2} & \text{if } \tau_2 < \tau < \tau_3, \\ k_2 & \text{if } \tau_3 \leqslant \tau, \end{cases} \tag{41}$$

where $\tau_1 < z < \tau_2 < \tau_3$ is assumed. This infectivity multiplier is shown in Fig. 7 for one particular choice of the parameters. It is worth noting that this infectivity profile will only crudely mimic the disease-dependent infectivity described at the beginning of this section. In order to model the real disease dependence, we would need to convolve our $\kappa(\tau)$ with the duration of infection distribution. This greatly complicates the analysis and, although convolving $\kappa(\tau)$ would change the

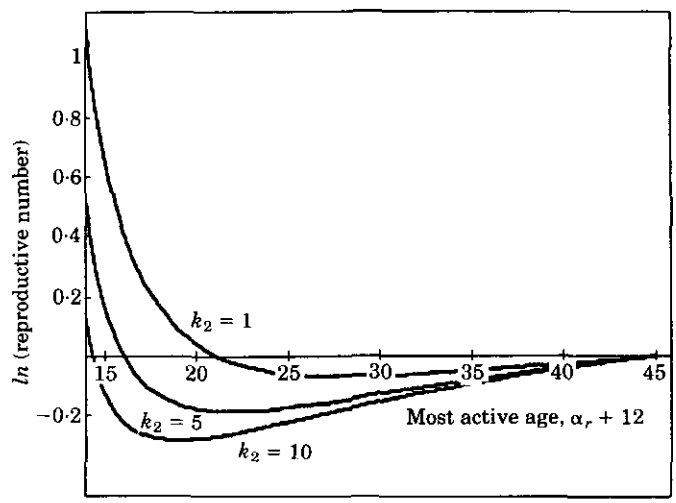

FIG. 8. The reproductive number (39) as a function of the most active age, for three different infectivity profiles. Shifting the infectivity late in infection decreases the probability that an epidemic will be able to get started, except when people are most sexually active at older ages. In each case, the infectivity profile is flat until 4 years after infection, rises linearly until 15 years, and then is constant again. There is no initial peak. The three cases represent the different ratios between the late and early values. The profile is constant in the upper curve, and the ratios are 5 and 10 for the lower curves, respectively. The most likely age of migration is 18, $\gamma = 0{\cdot}1$ yrs^{-1}, the average probability of transmission is 0·05, and the mean risk is 2 partners per year.

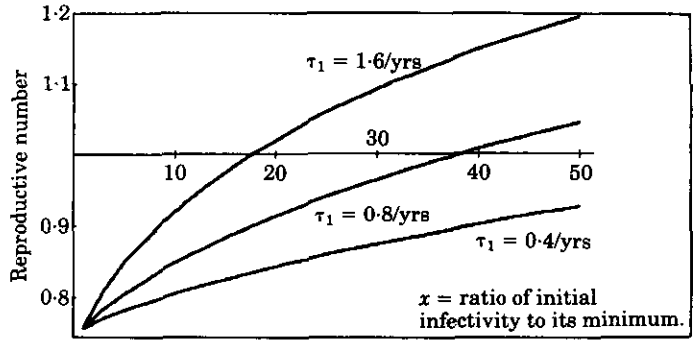

FIG. 9. The reproductive number (39) as a function of $x = e^{\tau_1/k_1}$, for three different widths of the initial peak. Concentrating the infectivity earlier in infection increases the probability that an epidemic will be able to get started. In each case, the infectivity profile drops exponentially from xq, to q, is flat until 4 years after infection, rises linearly to $10q$ at 15 years, and then is constant again. The value q is chosen to insure that the average probability of transmission is 0·05. All parameters except the infectivity profile are the same as in Fig. 8.

details of the infectivity profile, it would have only a small impact on our conclusions.

Figures 6–9 show the impact that the functional dependence on the duration of infection can have on the reproductive number. In each set of figures the mean infectivity is taken to be 0·05 per partner, the mean risk is 2 partners/yr and $\mu = 1/15\ \text{yrs}^{-1}$, as in example (ii). We also take $\alpha_m = 6$ yrs, so that 18 is the most likely age of migration.

In Fig. 6 we examine the impact of the delay, z, when the infectivity profile is independent of the duration of infection [$\kappa(\tau) = 1$]. We compare the no delay case of example (ii) ($z = 0$) with a 2-year delay ($z = 2$). In order to study only the effects of the functional form of the duration of infection distribution, we choose the two γ_1 parameters in such a way that in both cases the mean duration of infection is the same. For the 2-year delay, $\gamma_1 = 0{\cdot}1\ \text{yrs}^{-1}$, and for the 0 year delay, $\gamma_1 = 0{\cdot}094\ \text{yrs}^{-1}$. The calculations for this shift are given in the Appendix. Note that γ_1 increases with z, since the rate of developing AIDS after the delay must be faster in order to ensure that the mean duration of infection remains unchanged. The delay raises the reproductive number, as more people are infected for at least 2 years, and thus have an opportunity to infect someone else before developing AIDS. This shift brings the model close to threshold [$\ln(\bar{R}) = 0$] for the set of parameters chosen here.

In Fig. 8 and Fig. 9, we examine the dependence of the reproductive number on the infectivity profile. Taking $z = 2$, $\gamma_1 = 0{\cdot}1\ \text{yrs}^{-1}$, and all other parameters the same as for Fig. 6, we modify the infectivity multipler, $\beta = \beta_1$ in such a way that the mean infectivity stays constant at 0·05 per partner (see the Appendix). In Fig. 8, we assume that there is no initial peak ($\tau_1 = 0$), and look at the late profile. As the infectivity shifts more towards long durations of infection, the reproductive number decreases. Fewer infections are transmitted in the first few years after infection, and presumably there is a greater chance for chains of infection to be broken via deaths, even though the mean number of partners infected per person is the same.

Finally, in Fig. 9 we change the height of the initial peak, relative to the rest of the infectivity profile, as well as the width of the peak. This has a much smaller effect than the height of the later profile, presumably because the initial peak is fairly narrow. Since the changes in $\bar{R}$ are small, we plot the reproductive number instead of $\ln(\bar{R})$. As more of the infectivity shifts into the initial peak, the reproductive number increases. This is consistent with the findings above that the more likely it is that most infections are transmitted soon after infection, rather than late in disease, the greater the reproductive number will be, all other parameters (mean infectivity, mean duration of infection, mean risk) being equal.

Note that the impact of age-structure in this set of examples is somewhat greater than the impact of the duration of infection. Most models to date have concentrated on studying the impact of the duration of infection and the structure of risk, but it is possible that age actually plays an equally (if not more) important role in the dynamics of the epidemic.

4. Continuous Risk Model

We now generalize the discrete risk-group model of the previous section to allow for a continuous range in risk values. Let r be the rate of partner acquisitions, $U = U(t, a, r)$, $I = I(t, a, \tau, r)$, and $A = A(t, a)$.

Then

$$\begin{cases} \dfrac{\partial U(t,a,r)}{\partial t} + \dfrac{\partial U(t,a,r)}{\partial a} = \Lambda(a,r) - (\mu(a) + \lambda(t,a,r))U(t,a,r), \\ U(t,a_0,r) = B(r), \\ U(0,a,r) = \Phi(a,r); \end{cases} \tag{42a}$$

$$\begin{cases} \dfrac{\partial I(t,a,\tau,r)}{\partial t} + \dfrac{\partial I(t,a,\tau,r)}{\partial a} + \dfrac{\partial I(t,a,\tau,r)}{\partial \tau} = -(\mu(a) + \gamma(\tau,a))I(t,a,\tau,r), \\ I(t,a_0,0,r) = 0, \\ I(t,a,0,r) = \lambda(t,a,r)U(t,a,r), \\ I(0,a,\tau,r) = \Psi(a,\tau,r); \end{cases} \tag{42b}$$

$$\begin{cases} \dfrac{\partial A(t,a)}{\partial t} + \dfrac{\partial A(t,a)}{\partial a} = -\delta(a)A(t,a) + \displaystyle\int_0^\infty \int_0^{a-a_0} \gamma(\tau,a)I(t,a,\tau,r)\,d\tau\ dr, \\ A(t,a_0,r) = 0, \\ A(0,a,r) = 0. \end{cases} \tag{42c}$$

The infection rate is assumed to be

$$\lambda(t,a,r) = \int_0^\infty \int_{a_0}^\infty \int_0^{a'-a_0} \beta(a,a',r,r',\tau) \times \pi(t,a,a',r,r') \frac{I(t,a',\tau,r')}{N(t,a',r')} d\tau\ da'\ dr' \tag{43}$$

where

$$N(t,a',r') = U(t,a',r') + \int_0^{a'-a_0} I(t,a',\tau,r')\,d\tau, \tag{44a}$$

$$\beta(a,a',r,r',\tau) = s(r)f(r')\beta(a)\kappa(\tau), \tag{44b}$$

and

$$\pi(t,a,a',r,r') = \frac{n(a,r)n(a',r')N(t,a',r')}{\displaystyle\int_{a_0}^\infty \int_0^\infty n(\xi,\eta)N(t,\xi,\eta)\,d\xi\ d\eta}. \tag{44c}$$

Here, $n(a,r)$ is the total number of sexual contacts corresponding to $r_i(a)$ in eqn (33).

As before, threshold conditions are determined by studying the behavior of the model near the infection-free equilibrium $[U = U^0(a,r), I = 0, A = 0]$, where now

$$U^0(a,r) = B(r)e^{-M(a)} + e^{-M(a)} \int_{a_0}^\infty \Lambda(x,r)e^{M(x)}\,dx. \tag{45}$$

We approximate the infection rate as before,

$$\tilde{\lambda}(t,a,r) = \frac{s(r)n(a,r)}{\displaystyle\int_{a_0}^\infty \int_0^\infty n(\xi,\eta)U^0(\xi,\eta)\,d\xi\ d\eta} \times \int_0^\infty \int_{a_0}^\infty \int_0^{a'-a_0} f(r')n(a',r') \kappa(\tau)I(t,a',\tau,r')\,d\tau\ da'\ dr'. \tag{46}$$

This model is a special case of a model proposed by Busenberg and Castillo-Chavez (1991), if one allows the migration function Λ in their model to have a delta function at age a_0, and shifts age to be 0 at a_0. They give a threshold condition for the case $\beta(a', r', \tau)$, rather than the case described by eqn (44b).

The linearized equations are

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} = -\mu(a)u - \tilde{\lambda}(t,a,r)U^0(a,r), \tag{47a}$$

$$\begin{cases} \dfrac{\partial I}{\partial t} + \dfrac{\partial I}{\partial a} + \dfrac{\partial I}{\partial \tau} = -(\mu(a) + \gamma(\tau))I, \\ I(t,a,0,r) = \tilde{\lambda}(t,a,r)U^0(a,r), \end{cases} \tag{47b}$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} = -\delta(a)A + \int_0^\infty \int_0^{a-a_0} \gamma(\tau,r)I(t,a,\tau,r)\,d\tau\,dr. \tag{47c}$$

By proceeding as in previous sections, the stability of the infection-free equilibrium for the AIDS model eqn (42) is determined by the reproductive number

$$\bar{R} = \frac{\int_0^\infty s(r)f(r)\int_{a_0}^\infty n(a,r)\int_0^{a-a_0}\kappa(\tau)\beta(a-\tau)n(a-\tau,r)e^{-\Delta(a,r)}U^0(a-\tau,r)\,d\tau\,da\,dr}{\int_0^\infty\int_{a_0}^\infty n(a,r)U^0(a,r)\,da\,dr}. \quad (48)$$

5. Non-random Mixing

A number of modelers have demonstrated that biases in partner selection can have a major impact on the initial behavior of the epidemic and even change initial growth from exponential to polynomial (Jacquez *et al.*, 1988; Hyman & Stanley, 1988, 1989). Data on the sexual behavior of heterosexuals shows a strong age-bias in partner choice (UN, First Marriage paper, 1988; Giesecke *et al.*, 1990). The Longitudinal AIDS Impact Project found a similar bias in homosexual men (Morris, 1993). We relax the assumption of proportionate mixing in the final model of this paper and discuss the implications of partner selection on the threshold conditions and early epidemic growth. Although the results presented in this section could be generalized to multiple or continuous risk groups with duration of infection effects, to simplify the analysis we take the special case of a single risk group ($L = 1$) and no duration of infection. In this special case, we can drop the index i in eqn (1) and the rate of infection given by eqn (2) becomes

$$\lambda(t,a) = \int_0^\infty \beta(a,a')\pi(a,a',t)\frac{I(t,a')}{N(t,a')}\,da'.$$

We assume, as in Section 2, that

$$\beta(a,a') = \beta(a),$$

but generalize the expression [eqn (3)] for the rate of pair formation, $\pi(a,a',t)$, to allow sexual partners to be chosen in a biased manner.

We examine a special subset of biased-mixing functions. To motivate our choice of restrictions, note that eqn (3) can be rewritten in the form

$$\pi(a,a',t) = F[N,a]F[N,a']N(t,a'),$$

where

$$F[N,a] = \frac{r(a)}{\sqrt{\int_0^\infty r(x)N(t,x)\,dx}}$$

is a functional of the population distribution, N, and the age a. This expression shows that for random mixing $\pi(t,a,a')$ is *separable* into factors which are functions of either a or a', and whose only dependence on time is through the total population $N(t,a)$. This property of *separability* was crucial to the procedures used to determine the threshold conditions in the preceding sections of this paper.

In order to generalize these results to a larger class of mixing possibilities, suppose that $\pi(a,a',t)$ is a finite sum of separable terms:

$$\pi(a,a',t) = \sum_{i=1}^K F_i[N,a]G_i[N,a']N(t,a'), \quad (49)$$

where we assume that the t dependence is only through the total population, $N(t,a)$. Note that as $K \to \infty$ this sum can approximate all continuous functions of a and a'. The terms F_i and G_i cannot be chosen arbitrarily, because $\pi(a,a',t)$, the rate of contact per person of age a with people of age a', must satisfy three well-known mathematical constraints: (i) the total contact rate between ages a and a' is the per person rate multiplied by the population of age a, $\pi(a,a',t)N(a,t)$, but it is also $\pi(a',a,t)N(a',t)$, i.e.

$$\pi(a,a',t)N(a,t) = \pi(a',a,t)N(a',t); \quad (50a)$$

(ii) because we have assumed a contact rate per person of $r(a)$, we must have

$$\int_0^\infty \pi(a,a',t)\,da' = r(a); \quad (50b)$$

and (iii) the contact rates are non-negative

$$\pi(a,a',t) \geq 0. \quad (50c)$$

Substituting (49) into (50) gives

$$\sum_{i=1}^K F_i[N,a]G_i[N,a']N(t,a')N(t,a) = \sum_{i=1}^K F_i[N,a']G_i[N,a]N(t,a')N(t,a). \quad (51)$$

The arbitrary functional dependence of the F_i and G_i implies that [so long as $N(t,a)$ is non-zero] each term on the left-hand side of eqn (51) must equal a term on the right-hand side for all values of a, a', and $N(t,a)$, $N(t,a')$. In other words, for each index i, there is an index j for which

$$F_i[N(t,a),a]G_i[N(t,a'),a'] = F_j[N(t,a'),a']G_j[N(t,a),a], \quad (52)$$

and therefore $G_j[N, a] = F_i[N, a]$ for some index i. The resulting terms in the sum are either symmetric, (if i equals j, $F_i[N, a] = F_i[N, a']$) or can be rewritten in symmetric form:

$$\begin{aligned} &F_i[N, a]F_j[N, a'] + F_j[N, a]F_i[N, a'] \\ &\quad = \tfrac{1}{2}(F_i[N, a] + F_j[N, a])(F_i[N, a'] + F_j[N, a']) \\ &\qquad - \tfrac{1}{2}(F_i[N, a] - F_j[N, a])(F_i[N, a'] - F_j[N, a']). \end{aligned} \tag{53}$$

This allows us to assume that

$$\pi(a, a', t) = \sum_{i=1}^{K} g_i F_i[N, a]F_i[N, a']N(t, a'), \tag{54}$$

where $g_i = \pm 1$.

Constraints (50b) and (50c) imply that these terms must further be chosen to give a positive sum, π, and to satisfy:

$$r(a) = \sum_{i=1}^{K} g_i F_i[N, a] \int_0^\infty F_i[N(t, a'), a']N(t, a')\,da'. \tag{55}$$

Constraint (55) reduces the number of degrees of freedom in the system to $K - 1$. For example, if $K = 1$ random mixing is the only possibility. For $K = 2$, $\pi(a, a', t)$ must have the form

$$\begin{aligned} \pi(a, a', t) &= g_1 F[N, a]F[N, a']N(t, a') \\ &\quad + A^{-1}(t)q(a, t)q(a', t) \end{aligned} \tag{56}$$

where

$$\begin{aligned} q(a, t) &= r(t, a) - g_1 B(t)F[N, a], \\ B(t) &= \int_0^\infty F[N, x]N(t, x)\,dx, \\ A(t) &= \int_0^\infty r(x)N(t, x)\,dx - g_1 B^2(t), \end{aligned}$$

$g_1 = \pm 1$, and F are arbitrary, except for the requirement that π is non-negative.

A number of people (Castillo-Chavez & Blythe, 1989; Stanley *et al.*, 1990) have developed generic formulas for π which satisfy these constraints, but these formulas do not fall easily into our separable sum framework. Our assumptions lead to a very special case of mixing and we leave it to future study to determine how many terms of an expansion are necessary for approximating any predetermined mixing pattern.

Given eqn (54) for π, we then have that the rate of infection given in (4) is replaced by

$$\begin{aligned} \lambda(t, a) = \beta(a) &\sum_{i=1}^{K} g_i F_i[N(t, a), a] \\ &\times \int_0^\infty I(t, a')F_i[N(t, a'), a']\,da'. \end{aligned} \tag{57}$$

As before, we analyze the threshold conditions by linearizing our system of equations (1) and (57) around the trivial equilibrium. Substituting eqn (57) into eqn (1b) for the infected population and letting $U(t, a) = U^0(a) + e^{c(t-a)}\tilde{u}(a)$, $I(t, a) = e^{c(t-a)}\tilde{I}(a)$ leads to the linearized equation

$$\begin{aligned} \frac{\tilde{I}(a)}{da} = &-(\mu(a) + \gamma(a))\tilde{I}(a) + \\ &e^{ca}\beta(a) \sum_{i=1}^{K} g_i F_i[U^0(a), a]U^0(a)W_i, \end{aligned} \tag{58}$$

where the single quantity W in the earlier sections is replaced by a vector with components

$$W_i = \int_{a_0}^{\infty} \tilde{I}(a')F_i[U^0(a'), a']e^{-ca'}\,da'. \tag{59}$$

This equation has the solution

$$\tilde{I}(a) = \sum_{i=1}^{K} b_i(a, c)W_i. \tag{60}$$

where

$$\begin{aligned} b_i(a, c) = g_i \int_{a_0}^{a} &e^{cx}\mathrm{P}(x, a) \\ &\times \beta(x)F_i[U^0(x), x]U^0(x)\,dx\,da. \end{aligned}$$

Substituting (60) into (59) gives

$$W_i = \sum_{j=1}^{K} a_{ij}(c)W_j, \tag{61a}$$

where

$$a_{ij}(c) = g_i \int_{a_0}^{\infty} F_i[U^0(a), a]e^{-ca}b_j(a, c)\,da. \tag{61b}$$

This is a set of K equations in K unknowns, analogous to the single eqn (16) that gives the random-mixing threshold result.

Rewriting (61a) into matrix form gives

$$\mathbf{W} = \mathbf{A}(c)\mathbf{W}, \tag{62}$$

where $\mathbf{W} = (W_1, \ldots, W_K)$ and $\mathbf{A}(c) = (a_{ij}(c))$.

The eqn (62) has a non-zero solution only when

$$\det(\mathbf{A}(c) - \mathbf{I}) = 0. \tag{63}$$

The growth rates, c, are then restricted by this equation, which will have multiple roots. It is only when at least one of these roots has a positive real part that the infected population can grow when the population starts near the trivial equilibrium.

For the special case where the a_{ij} are all positive, we can now generalize the threshold results for random mixing. We state this as the following theorem:

Theorem: When the functions are chosen so that all of the a_{ij} *are positive, the reproductive number is the maximal eigenvalue of* $\mathbf{A}(0)$.

To prove this, note that eqn (63) is equivalent to $1 \in \sigma(\mathbf{A}(c))$ for some c, where $\sigma(\mathbf{A}(c))$ is the spectrum of $\mathbf{A}(c)$. Because all elements of $\mathbf{A}(c)$ are positive, the Perron–Frobenius theorem tells us that $\rho(\mathbf{A}(c))$ is a positive eigenvalue of $\mathbf{A}(c)$, and the moduli of all other eigenvalues are less than it. Hence, we only need to show that there exists a c such that $\rho(\mathbf{A}(c)) = 1$.

Denote $\mathbf{P} > \mathbf{Q}$ if $p_{ij} > q_{ij}$. Then it follows that $\rho(\mathbf{P}) > \rho(\mathbf{Q})$ from $\mathbf{P} > \mathbf{Q}$. Because $a_{ij}(c)$ in eqn (61b) are decreasing functions of c, we have that $\rho(\mathbf{A}(c))$ is a decreasing function of c. Using $\lim_{c\to\infty} \rho(\mathbf{A}(c)) = 0$, $\rho(\mathbf{A}(c)) = \lim_{n\to\infty} \|\mathbf{A}^n(c)\|^{1/n}$, and $\lim_{c\to-\infty} \mathbf{A}(c) = \infty$, it follows that $\lim_{c\to-\infty} \rho(\mathbf{A}(c)) = \infty$. Hence, from the continuity of $\mathbf{A}(c)$ for c, there exists a unique c such that $\rho(\mathbf{A}(c)) = 1$ and $\rho(\mathbf{A}(0)) < 1$ implies $c < 0$ and $\rho(\mathbf{A}(0)) > 1$ gives $c > 0$. This completes the proof of the theorem.

6. Discussion

We have determined the threshold conditions for a series of age-structured AIDS models. The threshold conditions, expressed in terms of the reproductive number, identify the qualitative relationships between the epidemiological parameters and the growth rate of the epidemic. Compared to the full solution of the system of integral/partial differential equations, these threshold conditions provide a simplified framework to identify the important factors that drive the epidemic, show how the epidemic may vary as conditions change, and can help suggest strategies for controlling the epidemic. The sensitivity of the reproductive number to both social and biological factors illustrates that these factors must be included in any realistic model of the epidemic.

The rate of infection is a key factor in the reproductive number. It strongly depends upon social mixing patterns and on how partnerships are formed. Most people do not select their partners randomly from all age and risk groups but prefer partners of similar age and risk behavior. In our earlier work we have numerically explored the impact of biased partner selection: here we have determined threshold conditions for a limited class of biased mixing models.

Through a series of specific parameter choices, we examined in more depth the dependence of the threshold condition on both the age-structure and the distribution of parameters with duration of infection. These examples show that the age-structure of human behavior may be one of the most important factors influencing the spread of the epidemic: in fact it may be more important than the shape of the survival curve describing the distribution of times from infection to AIDS, and the distribution of the infectivity with duration of infection. A great deal of effort has gone into the difficult task of determining the survival curve from a variety of data sets, none of which extend past 12 years after infection. Also, researchers have tried to collect data which will allow them to estimate the infectivity profile. It has unfortunately proven extremely difficult to gather information on human sexual behavior. Our work shows, once again, that without good information on this crucial aspect of the epidemic, it will be a long time before we may have any idea where this epidemic is going.

This research was supported by the Department of Energy under contracts W-7405-ENG-36 and KC-07-01-01.

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APPENDIX

Analysis of the Examples (ii) and (iii)

In this Appendix we derive the formulas for the figures in the main text.

ANALYSIS OF EXAMPLE (ii)

Substituting $B_i = 0$ and the rate of migration $\Lambda(a)$, defined by eqn (29), into eqn (5) for the equilibrium population gives

$$U_i^0(a) = 2^{-3i} C_m \int_{12}^{a} (x - 12) e^{-(x-12)/\alpha_m - \mu(a-x)}\, dx. \tag{A.1}$$

Note that we assumed a constant out-migration rate, μ, and a minimum age of $a_0 = 12$.

Integrating (A.1) gives

$$U_i^0(a) = 2^{-3i} \frac{\alpha_m C_m}{\alpha_m \mu - 1} \times \left(\left((a-12) - \frac{\alpha_m}{\alpha_m \mu - 1} \right) e^{-(a-12)/\alpha_m} + \frac{\alpha_m}{\alpha_m \mu - 1} e^{-\mu(a-12)} \right) \quad \text{for } \alpha_m \neq \frac{1}{\mu}. \tag{A.2}$$

Since $\Sigma_0^\infty 2^{-3i} = \frac{8}{7}$, summing and integrating $U_i^0(a)$ over all i and a gives the total population:

$$U_T^0 = \frac{8\alpha_m^2}{7\mu} C_m. \tag{A.3}$$

Figure 1 shows the normalized population distribution, $\Sigma_{i=0}^\infty U_i^0(a)/U_T^0$. Note that all risk groups have the same functional distribution in age, with the i-th group one-eighth the size of the $i-1$st risk group.

The mean risk of the total population is found by multiplying the i-th population, $U_i^0(a)$, by its risk $r_i(a)$, integrating over all a, and summing over all i, then dividing the result by U_T^0. Noting that $\Sigma_0^\infty 2^{-2i} = \frac{4}{3}$, this yields the mean population risk

$$\langle r^0 \rangle = C_r r_{base}(\alpha_r, \alpha_m, \mu), \tag{A.4a}$$

where we define

$$r_{base}(\alpha_r, \alpha_m, \mu) = \tfrac{7}{6}\alpha_r^4 \frac{\mu(\alpha_r + 3\alpha_m + 2\mu\alpha_r\alpha_m)}{(1+\mu\alpha_r)^2(\alpha_m+\alpha_r)^3}. \tag{A.4b}$$

The mean risk is linear in the parameter C_r, but its dependence on the most likely age of migration, $\alpha_m + 12$, and most active age, $\alpha_r + 12$ is more complex. In Fig. 2 we explore this dependence, by plotting the function r_{base}, which is the same as the mean risk for the case $C_r = 1$. Note that the entrance age has little impact on the mean risk unless the most active age is larger than 30.

The reproductive number is proportional to the population's mean risk, so that increasing partner acquisition rates at the population level affects the behavior of the model in a (relatively) straight-forward way. However, populations with the same mean risk can have different reproductive numbers, and it is important to determine how the age-structure of the population and the distribution of sexual behavior within a population affects the epidemic. Figures 3–5 explore this question.

Since the mean risk is proportional to C_r, and this constant does not impact the functional form of the risk functions, we let C_r vary with the other population/risk parameters in a way that ensures that the mean equilibrium risk is held fixed, at a value $\bar{r}$. Thus, in calculating Figs 3–9, C_r is taken to be

$$C_r = \bar{r}/r_{base}(\alpha_r, \alpha_m, \mu), \tag{A.5}$$

so that recalculation of $\langle r^0 \rangle$ with this new expression for C_r yields the desired result, $\langle r^0 \rangle = \bar{r}$.

Since the spread of infection is initially determined by the total levels of sexual activity, the number of people with a given risk times that risk is a very important quantity. This product, which we term the total partner acquisition rate, determines the number of new partners that are occurring in each age group. In Fig. 3, we show the distribution of total partner acquisition rates over age as a function of the most active age parameter, $\alpha_r + 12$. What is plotted is the product of the (now normalized) risk function and the normalized population distribution:

$$\sum_i \frac{r_i(a)U_i(a)}{U_T^0} = \sum_i 2^{-2i} \frac{7\mu\bar{r}}{8\alpha_m(\alpha_m\mu - 1)r_{base}} \times \left(\left((a-12) - \frac{\alpha_m}{\alpha_m\mu - 1} \right) \times e^{-(a-12)/\alpha_m} + \frac{\alpha_m}{\alpha_m\mu - 1} e^{-\mu(a-12)} \right) \times (a-12)e^{-(a-12)/\alpha_r}. \tag{A.6}$$

Carrying out the integrals for the reproductive number (with $C_r = \bar{r}/r_{\text{rbase}}$) gives

$$\begin{aligned} \bar{R} = {} & \tfrac{9}{7}\beta\bar{r}(1+\mu\alpha_r)^4(\alpha_m+\alpha_r)^6(72\alpha_m^2 + 32\alpha_m\alpha_r \\ & + 48\gamma\alpha_m^2\alpha_r + 100\alpha_m^2\mu\alpha_r + 4\alpha_r^2 + 16\gamma\alpha_m\alpha_r^2 \\ & + 32\alpha_m\mu\alpha_r^2 + 32\gamma\alpha_m^2\mu\alpha_r^2 \\ & + 42\alpha_m^2\mu^2\alpha_r^2 + \alpha_r^3(2\gamma + 3\mu + 4\gamma\alpha_m\mu \\ & + 6\alpha_m\mu^2 + 6\gamma\alpha_m^2\mu^2 + 6\alpha_m^2\mu^3)) \\ & \times (\alpha_r^2\mu(2\alpha_m+\alpha_r)^4(2+\alpha_m\mu)^3(1+\gamma\alpha_r \\ & + \mu\alpha_r)^2(\alpha_r + 3\alpha_m + 2\mu\alpha_r\alpha_m)^2)^{-1}. \end{aligned} \tag{A.7}$$

This reproductive number is plotted in Fig. 4, as a function of the most active age, $\alpha_r + 12$, and the migration parameter α_m.

In order to further show the possible impact of age structure on the spread of the epidemic, in Fig. 5 we compare the reproductive number with age-structure to the reproductive number that would occur if the effect of the age-structure were only to change the mean and variance of the risk. The Anderson *et al.* reproductive number, $\bar{R}_A$, is the product of the infectivity β and the second mean of the risk E_2 divided by the product of $\mu + \gamma$ and the mean risk. To find the second mean of the risk, we multiply $r_i(a)^2$ and $U_i(a)/U_T^0$ together, integrate over all a, and sum over all i. This gives

$$E_2 = C_r^2 E_{base}(\alpha_r, \alpha_m, \mu) \tag{A.8a}$$

where we define

$$E_{base}(\alpha_r, \alpha_m, \mu) = \tfrac{7}{2}\mu\alpha_r^5 \frac{24\alpha_m^2 + 8\alpha_m\alpha_r + 16\alpha_m^2\mu\alpha_r + \alpha_r^2 + 2\alpha_m\mu\alpha_r^2 + 3\alpha_m^2\mu^2\alpha_r^2}{(2\alpha_m+\alpha_r)^2(2+\mu\alpha_r)^3}. \tag{A.8b}$$

E_{base} would be the second mean of the risk if C_r were 1. Substituting (A.8a) into formula (19) for $\bar{R}_A$,

$$\bar{R}_A = \tfrac{18}{7}\frac{\beta E_2}{\bar{r}(\mu+7)} = \frac{\beta \bar{r} E_{base}(\alpha_r, \alpha_m, \mu)}{(\mu+\gamma)(r_{base}(\alpha_r, \alpha_m, \mu))^2},$$

$$\bar{R}_A = \tfrac{18}{7}\beta\bar{r}\frac{24\alpha_m^2 + 8\alpha_m\alpha_r + 16\alpha_m^2\mu\alpha_r + \alpha_r^2 + 2\alpha_m\mu\alpha_r^2 + 3\alpha_m^2\mu^2\alpha_r^2}{(\mu+\gamma)(2\alpha_m+\alpha_r)^2(2+\mu\alpha_r)^3} \times \frac{(1+\mu\alpha_r)^4(\alpha_m+\alpha_r)^6}{\alpha_r^3\mu(\alpha_r+3\alpha_m+\mu\alpha_r\alpha_m)^2}. \quad \text{(A.10)}$$

The reproductive number from (A.5) and the Anderson *et al.* reproductive number from (A.10) are compared in Fig. 5.

ANALYSIS OF EXAMPLE (iii)

In this example, the equilibrium populations and risks are the same as in example (ii), implying that the expression for the mean risk is given by eqn (A.4). However, now γ and κ are no longer constants, but instead depend on the duration of infection, τ. In order to decouple the effects of this τ dependence from magnitude effects, we need expressions for the mean duration of infection and the mean infectivity.

In example (ii), the mean duration of infection is $1/(\mu+\gamma)$, and the mean infectivity is simply β. For example (iii), the probability density distribution of exit times to AIDS is

$$G(\tau) = \frac{1}{\Gamma} e^{-\mu\tau - \int_0^\tau \gamma(x)\,dx}, \quad \text{(A.11)}$$

where

$$\Gamma = \int_0^\infty e^{-\mu\tau - \int_0^\tau \gamma(x)\,dx}\,d\tau.$$

The mean duration of infection, $\bar{\tau}$, is the integral over all τ of $\tau G(\tau)$. For example (iii):

$$\Gamma(\mu, \gamma_1, z) = \frac{1}{\mu}(1 - e^{-z\mu}) + \frac{1}{\gamma_1+\mu} e^{-z\mu}, \quad \text{(A.12)}$$

giving

$$\bar{\tau}(\mu, \gamma_1, z) = \frac{1}{\Gamma(\mu,\gamma_1)}\left(\frac{1}{\mu^2} + \left(\frac{1}{\gamma_1+\mu}\left(z + \frac{1}{\gamma_1+\mu}\right) - \frac{1}{\mu}\left(z+\frac{1}{\mu}\right)e^{-z\mu}\right)\right). \quad \text{(A.13)}$$

In Fig. 6 we show the impact of a 2-year delay ($z = 0$) on the reproductive number, when the infectivity is independent of the duration of infection. All parameters except z and γ_1 are the same in both cases. For the case $z = 2$ yrs, we took $\gamma_1 = 0{\cdot}1$ yrs^{-1}. For the case $z = 0$, $\gamma_1 = 1/\bar{\tau} - \mu$, and we set it equal to $0{\cdot}095$ yrs^{-1} in order to ensure the same mean duration of infection as for the case $z = 2$. The mean infectivity $\bar{\beta}$ is the integral over all τ of $\beta(\tau)G(\tau)$. For this example, this mean infectivity is

$$\bar{\beta} = \frac{\beta_1 K(\mu, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3)}{\Gamma(\mu, \gamma_1, z)}, \quad \text{(A.14a)}$$

where

$$K(\mu, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3) = \int_0^\infty \kappa(\tau) e^{-(\mu\tau + \int_0^\tau \gamma(x)\,dx)}\,d\tau = \frac{\mu k_1 - 1}{\mu(1+\mu k_1)} - \frac{\gamma_1 e^{-z\mu}}{\mu(\mu+\gamma_1)} + \frac{k_2 e^{z\gamma_1}(e^{-(\mu+\gamma_1)\tau_2} - e^{-(\mu+\gamma_1)\tau_3})}{(\mu+\gamma_1)^2(\tau_3-\tau_2)}. \quad \text{(A.14b)}$$

For Figs 8 and 9, we have chosen to fix the mean infectivity, $\bar{\beta}$, at $0{\cdot}05$ per partner. We do this mathematically by constraining the parameter β_1, which appears linearly in (A.14a), to vary with the other parameters. Inverting (A.14a) gives

$$\beta_1(\mu, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3) = 0{\cdot}05\frac{\Gamma(\mu, \gamma_1, z)}{K(\mu, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3)} \quad \text{(A.15)}$$

where Γ is given by (A.12) and K is given by (A.14b). This choice of β_1 then ensures that the duration of infection impacts are disassociated from the mean infectivity levels. As in example (ii), we also take C_r to be given by (A.5) in order to ensure that the mean risk is independent of the parameter choices.

The reproductive number for example (iii) is found by substituting our parameter choices into eqn (3). Before we do this substitution, let us rewrite eqn (3) in a different form.

First we change variables from a to $x = a + a_0$, and then change the order of integration. These two changes give

$$\bar{R} = \frac{1}{\langle r^0\rangle U^0_T}\sum_{j=1}^{L} s_j f_j \int_0^\infty \kappa(\tau)\int_\tau^\infty \times r_j(x+a_0)\beta(x+a_0-\tau)r_j(x+a_0-\tau) \times e^{-\int_0^\tau(\gamma(r,r+x+a_0-\tau)+\mu(r+x+a_0-\tau))\,dr} \times U_j^0(x+a_0-\tau)\,dx\,d\tau. \quad \text{(A.16)}$$

Making one more variable change to $y = x - \tau$ gives

$$\bar{R} = \frac{1}{\langle r_0 \rangle U_T^0} \sum_{j=1}^{L} s_j f_j \int_0^\infty \kappa(\tau) \int_0^\infty \times r_j(y+\tau+a_0)\beta(x+a_0) r_j(y+a_0) \times e^{-\int_0^\tau (\gamma(v,x+y+a_0)+\mu(v+y+a_0))\,dv} \times U_j^0(y+a_0)\,dy\,d\tau. \quad (A.17)$$

Next, note that for our example μ and $\beta = \beta_1$ are constant, γ is independent of age, and s_j and f_j are both 1. This gives

$$\bar{R} = \frac{\beta_1}{\langle r^0 \rangle U_T^0} \sum_{j=1}^{L} \int_0^\infty \kappa(\tau) \int_0^\infty r_j(y+\tau+a_0) r_j(y+a_0) \times e^{-\int_0^\tau \gamma(v)\,dv - \mu\tau} U_j^0(y+a_0)\,dy\,d\tau. \quad (A.18)$$

Substituting the functions $r_i(a)$ and $U_i^0(a)$ for our example into (A.18) yields

$$\bar{R} = D \int_0^\infty \kappa(\tau) e^{-\int_0^\tau \gamma(v)\,dv - (\mu + 1/\alpha_r)\tau} \int_0^\infty y(y+\tau) e^{-2y/\alpha_r} \times ((y-C)e^{-y/\alpha_m} + Ce^{-\mu y})\,dy\,d\tau, \quad (A.19)$$

where we define

$$C = \frac{\alpha_m}{\alpha_m \mu - 1}$$

and

$$D = \frac{\beta_1 C_r^2 C_m C \sum_{j=0}^{\infty} 2^{-j}}{\langle r^0 \rangle U_T^0}.$$

This constant D can be rewritten in terms of the parameters of this example by substituting the expressions calculated above for β_1, U_T^0, C_r, and $\langle r_0 \rangle$. Doing this gives

$$D = 0{\cdot}05 \times \frac{7\mu\Gamma(\mu,\gamma_1)C\bar{r}}{4\alpha_m^2 K(\mu,\gamma_1,k_1,k_2,\tau_1,\tau_2,\tau_3)(\langle r^0 \rangle(1,\alpha_r,\alpha_m,\mu))^2}. \quad (A.20)$$

Expanding expression (A.19) for the reproductive number allows us to separate the τ and y integrals:

$$\bar{R} = D\left(\int_0^\infty \kappa(\tau e^{-\int_0^\tau \gamma(v)\,dv - (\mu+1/\alpha_r)\tau}\,d\tau \int_0^\infty y^2 e^{-2y/\alpha_r} \times ((y-C)e^{-y/\alpha_m} + Ce^{-\mu y})\,dy + \int_0^\infty \tau\kappa(\tau) e^{-\int_0^\tau \gamma(v)\,dv - (\mu+1/\alpha_r)\tau}\,d\tau \int_0^\infty y\, e^{-2y/\alpha_r} \times ((y-C)e^{-y/\alpha_m} + Ce^{-\mu y})\,dy \right). \quad (A.21)$$

The first of these four integrals (two integrals over τ and two integrals over y) is the same as K, given by (A.14b), except that μ is replaced with $\mu + 1/\alpha_r$. We let the second integral over τ be denoted by J, and the two integrals over y be denoted by A and B. This gives the reproductive number plotted in Figs 8 and 9:

$$\bar{R} = D(K(\mu + 1/\alpha_r, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3)A + J(\mu + 1/\alpha_r, \gamma_1, k_1, k_2, \tau_1, \tau_2, \tau_3)B), \quad (A.22)$$

where we define A, B, and J as

$$A = \int_0^\infty y^2 e^{-2y/\alpha_r}((y-C)e^{-y/\alpha_m} + Ce^{-\mu y})\,dy = 6\left(\frac{\alpha_r\alpha_m}{2\alpha_m+\alpha_r}\right)^4 - 2C\left(\frac{\alpha_r\alpha_m}{2\alpha_m+\alpha_r}\right)^3 + 2C\left(\frac{\alpha_r}{2+\alpha_r\mu}\right)^3,$$

$$B = \int_0^\infty y\, e^{-2y/\alpha_r}((y-C)e^{-y/\alpha_m} + Ce^{-\mu y})\,dy = 2\left(\frac{\alpha_r\alpha_m}{2\alpha_m+\alpha_r}\right)^3 - C\left(\frac{\alpha_r\alpha_m}{2\alpha_m+\alpha_r}\right)^2 + C\left(\frac{\alpha_r}{2+\alpha_r\mu}\right)^2,$$

and

$$J(\mu,\gamma_1,k_1,k_2,\tau_1,\tau_2,\tau_3) = \int_0^\infty \tau\kappa(\tau)e^{\mu\tau + \int_0^\tau \gamma(x)\,dx}\,d\tau = \sum_{i=1}^{5} Q_i(\mu,\gamma_1,k_1,k_2,\tau_1,\tau_2,\tau_3).$$

Note that, as with K, the parameter dependence of J is shown because in expression (A.22) for the reproductive number, the parameter μ that appears in the definition of J is replaced by $\mu + 1/\alpha_r$. In order to express J, we further define the five duration-dependent integrals

$$Q_1 = \int_0^{\tau_1} \tau\kappa(\tau)e^{-\mu\tau + \int_0^\tau \gamma(x)\,dx}\,d\tau = \left(\frac{k_1}{1+\mu k_1}\right)^2(1 - e^{-(\mu+1/k_1)\tau_1}) - \frac{\tau_1 k_1}{1+\mu k_1}e^{-(\mu+1/k_1)\tau_1},$$

$$Q_2 = \int_{\tau_1}^{z} \tau\kappa(\tau)e^{\mu\tau + \int_0^\tau \gamma(x)\,dx}\,d\tau = \frac{1}{\mu}e^{-\tau_1/k_1}\left(\left(\tau_1 + \frac{1}{\mu}\right)e^{-\mu\tau_1} - \left(z + \frac{1}{\mu}\right)e^{-zu}\right),$$

$$Q_3 = e^{-\tau_1/k_1 + z\gamma_1}\int_z^{\tau_2} \tau\, e^{-(\mu+\gamma_1)\tau}\,d\tau$$

$$= \frac{e^{-\tau_1/k_1}}{\mu+\gamma_1}\left(\left(z+\frac{1}{\mu+\gamma_1}\right)e^{-z\mu} - \left(\tau_3+\frac{1}{\mu+\gamma_1}\right)e^{\tau\gamma_1-(\mu+\gamma_1)\tau_3}\right),$$

$$Q_4 = \frac{e^{\tau\gamma_1}(k_2-e^{-\tau_1/k_1})}{\tau_3-\tau_2}\int_{\tau_2}^{\tau_3}\tau(\tau-\tau_2)e^{-(\mu+\gamma_1)\tau}\,d\tau$$

$$= \frac{e^{\tau\gamma_1}(k_2-e^{-\tau_1/k_1})}{(\tau_3-\tau_2)(\mu+\gamma_1)}\left(\frac{1}{\gamma_1+\mu} \times\left(\tau_2+\frac{2}{(\gamma_1+\mu)}\right)e^{-(\mu+\gamma_1)\tau_2} - \left((\tau_3-\tau_2)\tau_2+\frac{2\tau_3+\tau_2}{\gamma_1+\mu} + \frac{2}{(\gamma_1+\mu)^2}\right)e^{-(\mu+\gamma_1)\tau_3}\right),$$

and

$$Q_5 = k_2\,e^{\tau\gamma_1}\int_{\tau_3}^{\infty}\tau\,e^{-(\mu+\gamma_1)\tau}\,d\tau$$

$$= \frac{k_2\,e^{\tau\gamma_1}}{\mu+\gamma_1}\left(\tau_3+\frac{1}{\mu+\gamma_1}\right)e^{-(\mu+\gamma_1)\tau_3}.$$

In Fig. 6, we look at the impact of z when the infectivity is independent of τ, by setting $\tau_1 = 0$ and $k_2 = 1$. In Fig. 8, we continue to assume that $\tau_1 = 0$, but allow k_2 to vary. In Fig. 9, we set up the parameters for $\kappa(\tau)$ in the following way:

$$k_1 = \tau_1 \ln(x) \quad \text{and} \quad k_2 = 10x,$$

so that the infectivity profile drops from β_1 at the start of infection of β_1/x at τ_1, stays at β_1/x until τ_2, and then linearly increases to $10\beta_1/x$ at τ_3. After that it is flat again. Recall that β_1 is varying with x in such a way that the mean infectivity stays constant at 0·05 per partner. Thus at x increases, more and more of the infectivity profile is contained in the times shortly after infection. Likewise, as τ_1 increases, more and more of the infectivity is also contained in the region shortly after infection, and it is also more likely that a new partner will be encountered during the initial infectious period.